Recommendations for Self-Report Outcome Measures in Vulvodynia Clinical Trials

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Objectives: Vulvodynia (idiopathic chronic vulvar pain) is a prevalent condition associated with significant and negative impacts in many areas of function. Despite the increased research interest in vulvodynia in recent years, recommendations for outcome measures for use in clinical trials are missing. The purpose of this paper, therefore, was to provide recommendations for outcome measures for vulvodynia clinical trials so that consistent measures are used across trials to facilitate between-study comparisons and the conduct of large multicenter trials, and to improve measurement of the multiple dimensions of vulvodynia.

Methods: Given that provoked vestibulodynia (PVD)—characterized by provoked pain localized to the vaginal opening—is the most common subtype of vulvodynia and the current main focus of clinical trials, this paper focused on recommended outcome measures in PVD clinical trials. The framework used to guide the selection of outcome measures was based on the one proposed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).

Results: The IMMPACT framework provided a well-suited guideline for outcome measure recommendations in PVD clinical trials. However, given the provoked presentation of PVD and the significant impact it has on sexuality, modifications to some of the IMMPACT recommendations were made and specific additional measures were suggested.

Discussion: Measures that are specific to vulvovaginal pain are ideal for adoption in PVD clinical trials, and many such measures currently exist that allow the relevant IMMPACT domains to be captured.

Key Words: clinical trials, outcome measures, IMMPACT, vulvodynia, provoked vestibulodynia

(*Clin J Pain* 2017;33:756–765)

Chronic vulvar pain is a distressing condition, affecting approximately 8% of women under the age of 40 years in the general population.[1] The 2015 Classification of Chronic Vulvar Pain[2] proposes 2 main categories: vulvar pain related to a specific disorder (eg, inflammatory, neoplastic, traumatic, infection related, neurological) and vulvodynia, defined as idiopathic vulvar pain of at least 3 months' duration. Research demonstrates that women with vulvodynia experience negative impacts in terms of their psychological well-being, relationship adjustment, sexual function, and quality of life (QOL).[3] In addition, women with vulvodynia often report other chronic pain conditions, including irritable bowel syndrome and fibromyalgia.[4] Recent data suggest that the prevalence of these comorbid pain conditions increases in relation to the severity of the vulvar pain.[5]

Despite the increased research interest in vulvodynia in recent years, agreed-upon outcome measures for use in clinical trials are sorely missing. This gap is surprising, given that major inroads have been made in chronic pain and health outcomes, with endeavors such as the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[6,7] and the Patient-Reported Outcomes Measurement Information System[8] (PROMIS; all PROMIS measures are freely available with registration at http://www.nihpromis.org/measures/availableinstruments). A guideline for outcome measures in vulvodynia clinical trials is necessary for many reasons, the most significant being that without them, studies will continue to use different outcome scales (eg, single items, nonvalidated measures, validated measures), leading to difficulties comparing results among studies and conflicting results between studies. In addition, to date, most controlled and uncontrolled trials include single, unidimensional outcomes (eg, focusing on only 1 aspect of pain) rather than capturing the multidimensional aspects of vulvodynia (eg, focusing on multiple measures of the pain experience and different facets of functional impact). Using IMMPACT recommendations as a guideline, self-report outcome measures for clinical trials in vulvodynia focusing on pharmacologic, surgical, psychosocial, or complementary and alternative treatments, will be suggested.

IMMPACT

The aim of IMMPACT is to provide guidelines for clinical trials in pain research to facilitate comparison and pooling of data, encourage more complete reporting of outcomes, simplify the preparation and review of research proposals and manuscripts, and allow clinicians to make informed decisions about the risks and benefits of treatment.[6,7] The findings of the initial IMMPACT consensus meeting resulted in 6 core and 8 supplemental domains to consider as outcomes.

Received for publication July 20, 2016; revised December 20, 2016; accepted October 24, 2016.

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DOI: 10.1097/AJP.0000000000000453

Given that vulvodynia is best conceptualized as a pain condition,[9] the IMMPACT recommendations seem to be the most relevant model from which to draw and can serve to unify the field in terms of common outcome measures. At a minimum, each of the core and some of the supplemental domains should be assessed in vulvodynia clinical trials the core domains are pain, physical and emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition, and the vulvodynia-relevant supplemental domains are role and interpersonal functioning, and coping.[6,7] Given that provoked vestibulodynia (PVD)—defined as provoked pain localized to the vaginal opening—is the most common subtype of vulvodynia[3] and the current main focus of clinical trials, this paper will pay specific attention to recommended outcome measures in PVD clinical trials. As the most common presenting symptom of women with PVD is provoked dyspareunia—pain during sexual activities that involve vulvovaginal pressure/penetration—several aspects of sexual function should be specifically assessed in this population (see the "Physical function" section). Recommendations will also be made for other PVD-specific outcomes measures that may be of clinical and research importance, depending on the particular outcome measures of the trial to be undertaken (see the "Other domains to consider" section).

In line with IMMPACT guidelines, our recommendations for outcome measures take into account the psychometric properties (eg, validity and reliability), issues related to practical application (eg, brevity, availability in multiple languages), and prior use in clinical trials as much as possible. Note that PVD-specific or vulvodynia-specific measures will be preferentially recommended above generic measures, and in some instances, both will be recommended. In these instances, if the generic measure adds information above and beyond the PVD-specific or vulvodynia-specific measure, validating its use for vulvodynia samples is suggested. In addition, some domains should be assessed with overlapping measures (eg, legacy and newly developed measures of depression) to establish psychometric properties of the newly developed measures; in this way, researchers and clinicians can examine the utility of these measures in PVD clinical trials, aiding in future recommendations for outcome measures.

Core Measures to Consider for PVD Clinical Trials

Pain

IMMPACT describes self-report measures as the "gold standard" in assessing outcome, as they reflect the inherently subjective nature of pain. In terms of specific aspects of the pain experience, IMMPACT recommends assessing intensity, quality, temporal pattern, and the use of rescue treatments.[7]

Pain Intensity. The term "pain intensity" refers to how strong the pain feels; it forms 1 part of the sensory aspect of the pain experience. There are multiple ways in which to assess pain intensity. IMMPACT suggests using an 11-point (0 to 10) numerical rating scale (NRS),[7] with the anchors being no pain (0) and pain as bad as you can imagine (10). The suggested instructions for the scale are: "Please rate your pain by indicating the number that best describes your pain on average in the last 24 hours."[7] Depending on the nature of the pain and the goals of the study, the instructions can be changed to, for example, "…in the past week" or "…the last time you attempted vulvovaginal penetration." NRSs have well-established reliability and validity,[10] and their flexibility allows for capturing provoked pain in "real time." For example, NRSs can be incorporated into physical examinations (eg, during the cotton-swab test, one essential component of the diagnostic process for PVD),[9] a common practice in vulvodynia studies[11–13]; in addition, they can be integrated into face-to-face interviews, online surveys, and paper-and-pencil questionnaires. They can also be modified to suit the type of pain under investigation. A patient with PVD can be asked to rate pain intensity during sexual activities involving vulvovaginal penetration and during nonsexual activities involving vulvovaginal pressure (eg, wearing tight-fitting undergarments or clothing, cycling).

The most commonly used pain intensity rating scales in the vulvodynia literature are 11-point NRSs.[14–16] In women with PVD, pain intensity ratings during sexual activities involving vulvovaginal penetration are the most clinically meaningful functional outcome; however, tampon insertion and removal have been used as a surrogate outcome measure because sexual intercourse may be too painful for some women.[17] Women with PVD typically report their pain experienced in the preceding month (or past 4 attempts if there have been no penetrative sexual encounters in the preceding month) with the following anchors: no pain at all (0) and worst pain ever felt (10). This measure detects significant treatment effects in women with PVD[14–16,18,19] and demonstrates a significant positive correlation with other measures of pain intensity.[11]

IMMPACT also suggests the use of verbal rating scales (VRSs) as an additional outcome measure of pain intensity,[7] which have demonstrated validity and reliability in different pain populations.[10] Using instructions such as those mentioned above, VRSs usually offer a few discrete, descriptive choices for pain intensity, such as: none, mild, moderate, and severe. Although not commonly used in vulvodynia clinical trials, researchers should consider incorporating VRSs when appropriate. The Vulvar Pain Assessment Questionnaire (VPAQ)[20] is specific to those with vulvar pain, demonstrating both convergent and discriminant validity. Using the VPAQ's 2 pain intensity VRSs (for average and worst pain intensity; 5-point scale: none, mild, moderate, severe, and worst possible) in the Pain Severity subscale (which consists of a total of 6 VRSs), in addition to an 11-point NRS of pain intensity (Table 1), is recommended.

Pain Quality and Affect. Pain quality refers to how the pain is described in terms of sensory descriptors (eg, burning, sore), and pain affect (unpleasantness) reflects the emotional response to the pain. IMMPACT recommends the assessment of both pain quality and affect in clinical trials.[7] To capture both, IMMPACT suggests using the Short-Form McGill Pain Questionnaire (SF-MPQ).[21] The SF-MPQ is reliable and well validated, and it has been translated into numerous languages.[22] The SF-MPQ contains 15 sensory (eg, hot-burning, tender) and affective (eg, tiring-exhausting, sickening) pain descriptors to yield a total score, as well as sensory and affective subscale scores. Its subscales have demonstrated treatment responsiveness in chronic pain[23] and vulvodynia[24–27] trials. In the PVD treatment outcome literature, the original McGill Pain Questionnaire (MPQ)[28] has also been used, demonstrating changes in its various subscales and/or other scores at posttreatment.[14,19,29,30] The MPQ includes 78 adjectives

TABLE 1. Recommended Core and Secondary Outcome Measures of Vulvovaginal Pain Characteristics in PVD Clinical Trials

Pain Characteristic	Recommended Core Outcome Measure/s	Secondary Outcome Measure/s
Pain intensity	11-point NRS, from no pain at all (0) to worst pain ever felt (10) based on vulvovaginal pain experienced during sexual activities (past month) The 2 VPAQ pain intensity 5-point VRSs of the Pain Severity subscale for average and worst vulvovaginal pain (in a typical month)[20]	
Pain quality and affect	Short-form McGill Pain Questionnaire[21] The VPAQ Pain Descriptor Scale, and the 4 VRSs related to pain unpleasantness and pain distress from the Pain Severity subscale[20]	
Pain temporality		Questions could be asked about specific activities/situations that might provoke the pain of PVD (eg, penetrative intercourse, finger insertion, friction with clothing, tampon insertion), and pain intensity could be rated on an NRS or VRS. One study examined 12 such activities/situations in terms of the percentage of painful activities from pretreatment to posttreatment[18] In addition, the VPAQ includes 1 question on when the pain occurs to assess whether it is provoked, unprovoked, or both, and 1 additional question on the pattern of provoked pain[20]

NRS indicates numerical rating scale; PVD, provoked vestibulodynia; VPAQ, Vulvar Pain Assessment Questionnaire; VRS, visual rating scale.

describing various types of pain. Four subscales can be derived that describe the sensory (eg, burning, sore, stinging), affective (eg, tiring, grueling, suffocating), evaluative (eg, annoying, miserable, unbearable), and miscellaneous (eg, cool, radiating, nagging) aspects of pain. It also includes questions on pain location as well as a VRS of present pain intensity. When comparing both MPQs—which can be applied to any kind of pain—the SF-MPQ is briefer, more reader friendly, and specific to pain quality and affect. As such, its inclusion in PVD clinical trials is recommended. However, the VPAQ Pain Descriptors subscale and the 4 VRSs related to pain affect from the Pain Severity subscale[20] should also be incorporated. The Pain Descriptors subscale consists of 10 adjectives spanning burning, incisive, and sensitivity descriptors rated on a 5-point VRS (not at all, a little, somewhat, a lot, very much). The Pain Severity subscale includes a total of VRSs for pain affect, specifically, pain unpleasantness, and distress (average and worst pain unpleasantness/distress; none, mild, moderate, severe, worst possible).

Temporal Pattern of Pain (Temporality). Temporality refers to the pattern of the pain over time. It includes information pertaining to changes in pain intensity, as well as the frequency, duration, and intensity of pain episodes, and the frequency of "breakthrough" pain episodes.[7] IMMPACT recommends administering pain temporality scales as secondary outcome measures; however, no specific questionnaires are recommended.[7] Pain temporality is especially relevant for those who experience spontaneous/unprovoked pain. However, its application to PVD—a provoked pain condition—is limited: a validated PVD pain temporality questionnaire does not exist, and temporality is not commonly reported as an outcome in these trials. Thus, measures of pain temporality should also be considered as secondary in PVD clinical trials; investigators should create and validate their own measure (see Table 1 for suggestions). Yet, it is strongly recommended that vulvodynia studies take into account pain onset (ie, whether the pain has always been experienced [primary] or if it developed after a pain-free period of time [secondary]) given that some evidence suggests that those with primary PVD may benefit less from treatment[31]; in addition, pain onset figures prominently in the most current terminology for vulvodynia.[2]

Physical Function

Physical function measures typically assess multiple aspects of function, including sleep disturbance and impact on activities of daily living,[7] within a larger conceptualization of health-related quality of life (HRQOL). These measures can be generic or disease specific (Table 2). IMMPACT recommends the SF-36 Health Survey,[32] the most commonly used generic measure of HRQOL.[7] The SF-36 Health Survey has 36 items spanning 8 subscales: physical functioning, role functioning difficulties caused by physical problems, bodily pain, general health, vitality, social functioning, role functioning difficulties caused by emotional problems, and mental health. Although widely used to assess HRQOL in many conditions, the SF-36 Health Survey has not been frequently used in PVD clinical trials, likely because of the provoked nature of the pain. However, researchers are still urged to consider its use as a core measure in PVD clinical trials given that it has been used in several PVD studies[41,42] and that PVD is associated with many comorbidities (eg, depression, other pain conditions[4]) that can affect HRQOL; the validated PROMIS Global Health (10 items) and/or the Physical Function (10 items) Scales[8] are also recommended as secondary measures for those who are interested in establishing their validity for use in PVD clinical trials.

TABLE 2. Recommended Core and Secondary Outcome Measures Related to HRQOL in PVD Clinical Trials

Physical Function	Recommended Core Outcome Measure/s	Secondary Outcome Measure/s
Generic measure focusing on HRQOL	SF-36 Health Survey[32]	PROMIS Global Health Scale[8] The PROMIS Physical Function Scale[8]
Specific measures related to the effects of the pain on physical/other function		Interference Scale of the Multidimensional Pain Inventory[33] Pain interference items of the Brief Pain Inventory[34] The PROMIS Pain Interference Scale[8]
Specific measures related to the effects of vulvovaginal pain on physical/other function	Vulvodynia Quality of Life Scale[35,36] Life Interference subscale of the VPAQ[20]	
Sexual function	Female Sexual Function Index[37] Self-Penetration Interference subscale of the VPAQ[20]	The PROMIS SexFS Scale[38]
Sexual satisfaction		Global Measure of Sexual Satisfaction[39] The PROMIS SexFS Scale[38]
Sexual distress		Female Sexual Distress Scale[40]
Sexual function interference		VPAQ Sexual Function Interference Subscale[20]

HRQOL indicates health-related quality of life; PROMIS, Patient-Reported Outcomes Measurement Information System; PVD, provoked vestibulodynia; VPAQ, Vulvar Pain Assessment Questionnaire.

For assessing the specific effects of one's pain on physical function, IMMPACT recommends using either the Interference Scale of the Multidimensional Pain Inventory[33] or the pain interference items (general activity, mood, walking, work, social relations, sleep, and life enjoyment) of the Brief Pain Inventory[34]—or both if possible. These questionnaires assess general life domains that are usually affected in patients who have unprovoked pain and might be more relevant for the effects of comorbid pain conditions in those with PVD. Thus, their use as secondary measures in PVD clinical trials is recommended. An additional secondary measure for the purpose of validation could be the PROMIS 4-, 6-, or 8-item Pain Interference Scale.[8] However, to assess pain interference specifically due to vulvovaginal pain, the inclusion of the Vulvodynia Quality of Life Scale (VQOLS), which has been used in 2 cross-sectional vulvodynia studies to date,[35,36] and the Life Interference subscale of the VPAQ[20] are strongly recommended as core outcome measures. The VQOLS is an adapted version[35] of the well-validated Skindex-29,[43] a measure of QOL for those with skin disease. The VQOLS includes 15 items to assess the emotional (eg, "I am frustrated by my vulvovaginal pain" and "I am ashamed of my vulvovaginal pain") and functional (eg, "My vulvovaginal pain interferes with my sex life" and "My vulvovaginal pain affects how close I can be with those I love") dimensions of women's QOL, in addition to an "other" dimension (eg, "My vulvovaginal pain makes me feel lonely"), during the previous 4 weeks. Participants respond on a 10-point Likert-scale (10 = no effect to 100 = maximum effect). In addition, the 6-item Life Interference subscale of the VPAQ[20] assesses how much one's vulvovaginal pain negatively interferes with activities such as sitting, wearing tight-fitting clothing, and sleeping on a 5-point VRS (not at all, a little, somewhat, a lot, very much, and I avoid because of the pain).

Sexual Function, Satisfaction, Distress, and Interference

Given that many aspects of sexuality are negatively affected in those with PVD,[3] specific measures of sexual function, satisfaction, distress, and interference should be included as endpoints in PVD clinical trials. The most commonly used validated measure of sexual function in women with vulvodynia is the psychometrically sound Female Sexual Function Index (FSFI).[37] The FSFI is a 19-item, multidimensional, self-report measure comprised of 6 subscales related to sexual function (ie, desire, arousal, lubrication, orgasm, satisfaction, and pain) over the past 4 weeks. Each subscale yields a score, and a total score can also be obtained. A clinical cut-off score of 26.55 has been found to differentiate between women with and without sexual dysfunction.[44] The FSFI exhibits discriminant validity when examining sexual function women with vulvodynia as compared with asymptomatic women.[45] This measure was designed to measure sexual function in clinical trials, and it has been utilized in several PVD studies[11,42,46,47] and clinical trials[14,18,27]; thus, its use as a core outcome measure is recommended. Note that the scoring procedures of the FSFI have been criticized on the basis that women who have not engaged in sexual activities in the previous 4 weeks would have artificially low scores[48]; it has been recommended that, in these cases, the missing responses be coded as missing (as opposed to 0) and that the total score not be calculated. In addition, a specific PROMIS Sexual Function and Satisfaction (SexFS) Scale has recently been validated[38] (note that 1 item assesses erectile function in males but the other 10 items apply to both sexes); thus, it should be used as a secondary measure in PVD clinical trials to assess its applicability to women with vulvovaginal pain.

One aspect of sexual function that has not been frequently assessed is that of interference with solitary sexual activities involving vulvovaginal penetration. Such activities should be assessed in women with and without partners to understand the more general impact of having vulvovaginal pain; in addition, nonsexual penetrative activities (eg, tampon insertion) should also be evaluated. Therefore, the 5-item Self-Penetration Interference subscale of the VPAQ[20] should be considered a core outcome measure in PVD clinical trials.

Researchers should also consider using measures of sexual satisfaction, sexual distress, and sexual function interference as secondary outcome measures. The well-validated[49] Global Measure of Sexual Satisfaction[39] consisting of 5 items assessing global sexual satisfaction has been used in PVD studies[11,50] (note that the PROMIS SexFS

Scale[38] can be used concurrently to assess its applicability to PVD populations). The Female Sexual Distress Scale[40] is a 12-item measure assessing sexuality-related distress, which has been translated into numerous languages, and has demonstrated construct validity, internal consistency, 4-week test-retest reliability, and strong sensitivity to treatment response.[40] It has also been used in PVD studies.[51,52] In addition, the VPAQ[20] includes a 10-item Sexual Function Interference subscale that can be useful for the specific assessment of the pain's impact on sexual function.

Emotional Function

Because chronic pain is associated with psychological distress and mood disorders such as depression and anxiety,[53] IMMPACT suggests adding measures of emotional function.[7] PROMIS also provides measures of mental health, including depression and anxiety,[8] which have been validated across diverse clinical samples.[54] Self-report measures of depression and anxiety, as well as some other measures (eg, pain catastrophizing) should be considered core in vulvodynia clinical trials (Table 3).

Depression. Many studies have assessed depression by a range of methods (eg, a single question, a validated questionnaire). Generally, results have shown that although women with PVD demonstrate heightened levels of depressive symptoms as compared with pain-free control women, their scores are not typically in the clinical range.[61] The 2 most commonly used questionnaires to assess depression in the vulvodynia literature are the Beck Depression Inventory-II (BDI-II)[55]—a 21-item questionnaire assessing depressive symptoms over the past 4 weeks that has evidenced high internal consistency, high test-retest reliability (2 wk), and concurrent, content, and structural validity[62]—and the well-validated Center for Epidemiologic Studies Depression Scale (CES-D),[18,27] a 20-item scale measuring the frequency of depressive symptoms over the past week.[63] Although the BDI-II is recommended by IMMPACT, coadministration of the Profile of Mood States (POMS)[56] is also recommended given that the POMS provides a summary measure of total mood disturbance.[7]

TABLE 3. Recommended Core and Secondary Outcome Measures of Emotional Function

Emotional Function	Recommended Core Outcome Measure/s	Secondary Outcome Measure/s
Depression	Beck Depression Inventory-II[55]	Profile of Mood States if indicated (see text)[56] The PROMIS Depression Scale[8]
Anxiety	State-Trait Anxiety Inventory State subscale[57]	The PROMIS Anxiety Scale[8]
Emotional responses specific to vulvovaginal pain	The VPAQ Emotional Response subscale[20]	
Emotional responses to pain	Pain Catastrophizing Scale[58]	Pain Anxiety Symptoms Scale[59,60]

PROMIS indicates Patient-Reported Outcomes Measurement Information System; VPAQ, Vulvar Pain Assessment Questionnaire.

Indeed, it contains 6 subscales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Given that clinically relevant levels of depressive symptomatology are not commonly found in women with PVD, the BDI-II should be used as a core measure in PVD clinical trials, with the POMS as a secondary measure when participants score in the severe range (scores of 29 to 63[55]) on the BDI-II. An alternative (or supplemental) secondary measure is the PROMIS Depression Scale, as the scores on this 8-item measure correlate well with scores on the CES-D and the PHQ-9 (the 9-item Patient Health Questionnaire[64]), common measures of depressive symptomatology.[65]

Anxiety. Controlled studies show that women with vulvodynia report more anxiety than asymptomatic women, although typically not in the clinical range.[66] The most commonly used validated measure used to assess anxiety in women with vulvodynia[41,47,67] is the State/Trait Anxiety Inventory (STAI).[57] The STAI consists of 40 items divided into 2 sections, with 20 items measuring the transient condition of state anxiety and 20 items devoted to long-standing trait anxiety. Given its length and the fact that trait anxiety scores will likely not be affected by treatment, the administration of the 20-item State Anxiety subscale of the STAI as a core outcome measure is recommended. One of the short-form PROMIS Anxiety Scales[8] (4, 6, 7, or 8 items; preferably the 8-item scale) should also be used as a secondary measure for validation purposes.

Emotional Responses Specific to Vulvovaginal Pain. The Emotional Response subscale of the VPAQ affords a unique opportunity to tap into reactions such as sadness, tension, and stress with specific reference to the role of vulvovaginal pain. Items on this 14-item subscale are rated on a 5-point VRS (not at all, a little, somewhat, a lot, and very much).[20] This subscale is recommended as a core outcome measure in PVD clinical trials.

Pain Catastrophizing. Pain catastrophizing is a robust psychological predictor of pain and disability, and it is measured with the Pain Catastrophizing Scale (PCS),[58] which exhibits 6-week test-retest stability and discriminant validity, and has been used extensively in vulvodynia/PVD studies.[30,41,47,68] This 13-item measure assesses the thoughts and feelings experienced while in pain. Each item describes a different thought or feeling (eg, "It's terrible and I think it's never going to get any better"), and participants rate how frequently they experience each on a scale from 0 (not at all) to 4 (all the time). Three summed subscales are derived from this questionnaire: rumination, magnification, and helplessness. A total summed score is also calculated. High scores are indicative of an exaggerated negative orientation toward pain, with scores ranging from 0 to 52. A general cut-off score of 30 has been identified to separate those who catastrophize versus those who do not. Catastrophizing has been shown to be both responsive to treatment and predictive of worse treatment outcome,[14,18,69] strongly supporting the PCS as a core outcome measure in PVD clinical trials.

Pain Anxiety. Fear of pain contributes to the experience of pain and associated sexual impairment in women with vulvodynia.[70] The Pain Anxiety Symptoms Scale (PASS-20)[59] is a shorter version adapted from the original 40-item questionnaire.[60] It is a self-report measure of fear of pain designed for individuals with chronic pain problems and has been adapted for use in a sexual context[70]; it has also been used in the vulvodynia literature.[47,71] Items are

measured on a 6-point Likert scale with the endpoints never (0) and always (5). It includes 4 subscales: cognitive anxiety, escape/avoidance, fearful appraisal, and physiological anxiety. The PASS-20 has demonstrated good internal consistency (Cronbach α between 0.90 and 0.92), test-retest reliability, and a stable factorial structure.[59,72,73] The PASS-20 has also been found to be sensitive to change following treatment for chronic pain[74] and PVD.[69] Its use as a secondary outcome measure is recommended.

Participant Ratings of Global Improvement and Satisfaction With Treatment

Subjective assessments of participants' impression of change following treatment are required in pain clinical trials and most psychological intervention trials.[7] These measures were introduced in response to critiques concerning the extent to which statistically significant results reported in clinical trials were clinically relevant and meaningful in the lives of the patients.[7] The Patient Global Impression Change Scale (PGIC)[75] is a 7-point rating scale with the options very much improved (score of 1), much improved (2), minimally improved (3), no change from baseline (4), minimally worse (5), much worse (6), and very much worse (7). There has been widespread use of the PGIC in chronic pain clinical trials and the measure provides a responsive and readily interpretable assessment of participants' evaluations of the importance of their improvement or worsening. This scale has been adapted to women with vulvodynia to assess subjective improvements in both the pain and sexuality domains, and is sensitive to treatment changes.[76] This measure is an important indicator of the clinical significance of findings reported in clinical trials; thus, it is recommended as a core outcome measure for PVD clinical trials. Treatment satisfaction has also been measured in PVD clinical trials using, for example, an 11-point NRS (0 = completely dissatisfied to 10 = completely satisfied[76]); this scale should also be considered a core measure. Participant ratings of global improvement and satisfaction with treatment should be measured at posttreatment and later follow-ups.

Symptoms and Adverse Events

Monitoring symptoms and adverse events over the course of a clinical trial is important to estimate the safety of a given management strategy and to document whether some patients get worse, or experience temporary or permanent negative reactions to treatment.[7] In PVD clinical trials, this monitoring can take the form of weekly phone calls by a project coordinator to monitor adverse events, weekly check-ins completed by a therapist on a standardized form, or weekly completion of a brief online measure either on a study website or sent through email to study participants. The incidence of individual adverse events and serious adverse events should be reported for each treatment group, including the percentage of participants who experienced adverse events for a given management strategy. Active capture by structured interviews or questionnaires to assess specific symptoms and adverse events may be more useful than passive capture; therefore, active capture methods should be worked in at regular intervals throughout a trial, including at posttreatment and later follow-ups when possible.

Participant Disposition

IMMPACT recommends collecting and reporting comprehensive information on participant disposition, including data on recruitment and progression through the trial,[7] through the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[77] Examples of information that would be collected are the number of participants who withdrew/or were lost to follow-up and reasons for withdrawal/loss, number of excluded participants and reasons why, number of those who chose not to participate and why, and the types, rates, and reasons for treatment nonadherence.[7]

Supplemental Measures to Consider for Vulvodynia Clinical Trials

IMMPACT also urges researchers to consider including measures that tap into supplemental domains for clinical trials of chronic pain.[6] The following domains seem especially relevant to PVD clinical trials: Role function, interpersonal functioning, and coping (Table 4). Measures for other relevant domains to consider are also recommended (Table 5).

Role Function, Sexual Role Function, and Impact of the Pain on Sexual Role Function

Research has demonstrated that many women with vulvodynia experience adverse effects on their lifestyle[84] and report feeling like an inadequate woman/professional/partner.[85] Unfortunately, the domain of social role function has not yet been examined as a whole in PVD clinical trials. PROMIS offers a comprehensive scale assessing one's satisfaction with social role participation[8] that is recommended. This scale consists of questions related to, for example, satisfaction with one's ability to do things for their family, satisfaction with the amount of time spent at work and the quality of their work, and satisfaction with one's ability to do chores. Participants are asked to respond to these items on a 5-point scale from not at all to very much with the past week in mind.

Specific to the sexual impact of PVD, a recently published scale assesses one's feelings of self-worth related to maintaining a sexual relationship with their partner. The Sexual Contingent Self-Worth Scale (SCSWS)[78] is an 8-

TABLE 4. Supplemental Domains to Consider in PVD Clinical Trials and Suggested Measures

Domain	Suggested Measure/s
Role function	Social role: The PROMIS Social Role Participation Scale[8]
	Sexual role: Sexual Contingent Self-Worth Scale[78]
	Sexual role and how it is affected by vulvovaginal pain: the VPAQ Cognitive Response subscale[20]
Interpersonal functioning	Generic: 14-item Dyadic Adjustment Scale[79]
	Related to vulvovaginal pain: the VPAQ Partner Factors subscale[20]
Coping	Coping related to vulvovaginal pain: the VPAQ Coping subscale[20]
	Self-efficacy related to vulvovaginal pain: the Painful Intercourse Self-Efficacy Scale[69]

PROMIS indicates Patient-Reported Outcomes Measurement Information System; PVD, provoked vestibulodynia; VPAQ, Vulvar Pain Assessment Questionnaire.

TABLE 5. Other Measures to Consider in PVD Clinical Trials

Measure	Sample Item/s	No. Items and Scale Information
Body Image Scale[80]	"Have you been feeling self-conscious about your appearance?" (during the past week)	10 items 4-point scale: not at all, a little, quite a bit, very much
Body Exposure During Sexual Activity Questionnaire[81]	"During sexual activity I am thinking that my partner will notice something about my body that is a turn-off"	28 items 5-point scale: never, rarely, sometimes, often, always or almost always
The Female Genital Self-Image Scale[82]	"I feel positively about my genitals"	7 items 4-point scale: strongly disagree, disagree, agree, strongly agree
Vaginal Penetration Cognition Questionnaire[83]	Five subscales: Control cognitions: "I am afraid that I can have no influence on what happens during penetration" Catastrophic and pain cognitions: "I think about everything that can go wrong and fail with penetration" Self-image cognitions: "I am a poor partner when penetration fails" Positive cognitions: "Penetration will be pleasurable" Genital incompatibility: "I am afraid that my vagina is too narrow for penetration"	40 items 7-point scale from not at all applicable to very strongly applicable

PVD indicates provoked vestibulodynia.

item questionnaire assessing sexual contingent self-worth (SCSW) by 2 subscales: SCSW based on positive sexual events in the relationship, and SCSW based on negative sexual events in the relationship. Items are rated on a scale of 1 (not at all like me) to 5 (very much like me) and statements include the following: "I feel better about myself when it seems like my partner and I are sexually connected" and "When my sexual relationship is going bad, my feelings of self-worth remain unaffected" (reverse scored). The authors have demonstrated that the SCSWS exhibits good construct validity, incremental validity, internal consistency, and 2-week test-retest reliability.[78] Although it has not yet been used in vulvodynia/PVD studies given its recent publication, its use in such studies should be considered given its specificity to the sexual impact of vulvodynia/PVD. In addition, the Cognitive Response subscale of the VPAQ[20] taps into cognitions about one's role as a sexual partner that are specifically affected by vulvovaginal pain. This 8-item subscale asks, "In the past 6 months, how much do you experience thinking/worrying about the following related to your vulvar pain?" and includes items such as "That I am a bad sexual partner" and "That I will not be able to find a sexual partner." Responses are provided on a 5-point scale from not at all to very much. This measure should also be strongly considered for use in PVD clinical trials.

Interpersonal Functioning

Chronic pain affects partners, and partners can impact treatment outcomes reported by patients.[86] This pattern has also been demonstrated in coupled women with vulvodynia.[87] Thus, examining relationship adjustment as a supplemental domain in vulvodynia clinical trials is warranted. The Couple Satisfaction Index (CSI)[88] is a 32-item measure of relationship satisfaction that is appropriate for cohabiting as well as noncohabiting couples, whereas the Dyadic Adjustment Scale (DAS) (32 items)[89] is widely used for married or cohabiting couples, including its 14-item revised version.[79] The Relationship Assessment Scale is a brief measure (7 items) assessing relationship satisfaction[90] that should be considered as an alternative to the CSI/DAS if brevity is necessary. Of the measures mentioned, the DAS seems to be the most commonly used relationship scale in the vulvovaginal pain literature.[12,36,87,91] Finally, the VPAQ Partner Factors Scale[20] assesses negative partner responses (5 items), supportive partner response (7 items), the impact of vulvar pain on the relationship (6 items), and comfort with sexual communication (6 items) specifically related to one's experience of vulvovaginal pain. A brief, generic measure of relationship satisfaction—the 14-item DAS given its high internal consistency, and construct and discriminant validity[88,92]—and the VPAQ Partner Factors Scale,[20] which is specific to those with vulvovaginal pain, are recommended.

Coping

Pain coping refers to how one actively manages the pain. Several pain coping scales exist; however, assessing coping specifically in response to vulvovaginal pain is recommended. Thus, the Coping subscale of the VPAQ[20] is recommended. It consists of 12 items, 6 of which form a distraction/relaxation component (eg, "To cope with vulvar pain, I do something that takes my mind off the pain") and six of which form a problem-solving strategies component (eg, "To cope with my vulvar pain, I talk to others with similar pain").

Pain coping is highly related to pain self-efficacy,[93] usually defined as one's confidence in the ability to deal with symptoms, stresses, or limitations associated with a pain condition.[94] Pain self-efficacy in vulvodynia can be assessed using the Painful Intercourse Self-Efficacy Scale (PISES),[69] which was adapted from the Arthritis Self-Efficacy Scale.[95] The PISES consists of 20 items with 3 subscales: self-efficacy for controlling pain during intercourse, for sexual function, and for other symptoms. Women indicate their perceived ability to carry out sexual activities or to achieve outcomes in pain management by responding on a scale from 10 (very uncertain) to 100 (very certain). The reliability and validity of the original measure have been established,[95] and the factor structure of the adapted version has been shown to be identical to that of the original, with Cronbach α ranging from 0.79 to 0.89.[70]

Other Domains to Consider

Measures that assess function in domains other than those set out as core and supplemental by IMMPACT can also be important to consider when designing vulvodynia clinical trials (Table 5). The table is not meant to list all possible measures for use in vulvodynia clinical trials; rather, it represents a sample of measures to consider depending on the specific domains targeted by treatments used in the clinical trial. These include reliable and valid measures of body image, body self-consciousness during sexual activity, genital self-image, and cognitions about vaginal penetration,[80–83] all of which have been used in studies of women with vulvovaginal pain.[42,47,96–98] In addition, although not a specific dimension of vulvodynia or PVD, 1 clinical issue deserving of attention in clinical trials is the presence of comorbid pain conditions. Up to 45% of women with vulvodynia report a comorbid pain condition, and having a comorbidity is associated with increased feelings of isolation and invalidation.[99] In 1 study, irritable bowel syndrome and fibromyalgia were the most common comorbidities regardless of type of vulvodynia.[5] More recently, a population-based study involving 393 women who screened positive for vulvodynia aimed to identify empirically derived subgroups. Results showed that the presence or absence of spontaneous pain and the presence or absence of comorbid pain conditions differentiated between subgroups. The small proportion of women (16%) characterized by both spontaneous pain and comorbid pain conditions fared worse than other women with vulvodynia in terms of overall health, sleep, pain interference, physical pain, depression, and posttraumatic stress disorder.[100] Taken together, these findings suggest that women with vulvodynia who report a comorbid pain condition may present distinct clinical features that could influence their treatment responsiveness in clinical trials, and thus indicate that such comorbidities should, at the very least, be documented.

DISCUSSION

The aim of this review was to provide recommendations for self-report outcome measures in PVD clinical trials, with the goal of (1) unifying measures used across trials to facilitate between-study comparisons and the conduct of large multicenter trials, and (2) to improve measurement of the many dimensions of vulvodynia, taking into account its multiple biopsychosocial aspects. Ideally, a single validated questionnaire or repository would exist that covers all of the recommended domains for PVD clinical trials. No such questionnaire/repository exists at this time. However, the VPAQ comes close as a disease-specific set of scales designed to capture the biopsychosocial nature of chronic vulvovaginal pain.[20] It consists of multiple scales that can be administered together, or individually to target specific domains. These scales assess various aspects of the PVD experience: pain intensity, quality, affect; physical functioning (interference with life, self-penetration, and sexual function); emotional responses; coping; and the effects of the pain on sexual role function and interpersonal functioning. These questions span 3 core (pain, physical function, emotional function) and 3 supplementary domains (impact on sexual role function, interpersonal function, and coping) as identified by IMMPACT.[6,7] The application of this measure, in conjunction with others—including some PROMIS and other measures—to PVD clinical trials would be beneficial in terms of unifying the metric of outcome measurement.

From a larger perspective, patient-centered medicine and shrinking health care dollars are converging on the practice of medicine, dentistry, psychology, and other health care disciplines. What is emerging is the practice of health care through the use of evidence-based clinical pathways arrived at by clinical trials' results. These objectively derived clinical pathways will soon dictate management strategies for most medical conditions, including pain conditions. Assessing multiple parameters during clinical trials to customize the optimal treatment strategy is key to this process.

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